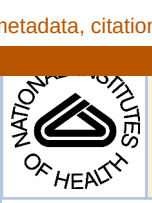

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Intima-media thickness and age of first depressive episode

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Abstract

Background—Late life depression, including patients with vascular depression, has been associated with higher levels of intima-media thickness (IMT). Although individuals with vascular depression tend to report a later onset of depression, the relationship of IMT and age of first depressive episode is uncertain in younger adults. We therefore investigated the relationship between IMT and age of first depressive episode in a sample of 202 adults (age range 40−81 years) with major depression (MDD).

Methods—Depression status was assessed using the Structured Clinical Interview Schedule and the Hamilton Depression Rating Scale. Patients underwent a physical examination in which a medical history was obtained. IMT was measured from the left and right common carotid arteries. Simple regression analyses were used to investigate the association between IMT and self-reported age of first depressive episode.

Results—IMT was associated with a later onset of first major depressive episode (b = .225, P = .0005) and this association remained significant after controlling for age, Framingham Stroke Risk Profile, smoking pack years, physical activity, high- and low-density lipoprotein, body mass index, triglyceride levels, and history of chronic medical conditions (b = .142, P = .028). Each .10 mm increase in IMT was associated with a 2.6-year later reported occurrence of first major depressive episode (MDE). Similarly, higher levels of IMT were associated with fewer previous MDEs (b = −.149, P = .020) and this effect remained significant in our multivariate model (b = −.140, P = .030). In contrast, IMT was not associated with current depressive severity (b = −.024, P = .720).

Conclusions—Greater levels of IMT are associated with a later onset of depression and fewer previous depressive episodes among middle-aged and older adults, independent of cardiovascular co-morbidities. These findings provide preliminary evidence that increased vascular burden may be associated with a later onset of depression.

Keywords

Intima-media thickness; Vascular disease; Depression; Vascular depression

1. Introduction

Major depression (MDD) is one of the primary causes of disability in the United States (Simon, 2003) and is associated with significant cardiovascular morbidity (Barnes et al., 2006).

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Conflict of interest

Dr. Doraiswamy has received grants and honoraria from several pharmaceutical companies.

Individuals experiencing MDD in later life exhibit a greater prevalence of *vascular depression* (Mast et al., 2008), characterized by poorer vascular health, cognitive decrements, and a later onset of first depressive episode, typically occurring after age 50 (Kim et al., 2006). Recent studies have demonstrated that individuals with a later onset of first MDE exhibit greater intima-media thickness (IMT), a marker of systemic atherosclerosis, compared with controls (Chen et al., 2006).

Despite evidence that individuals with vascular depression exhibit a later onset of first depressive episode and greater vascular burden, the mechanisms responsible for the characteristic later onset of this disorder have received little attention. It has been hypothesized that poorer vascular health results in greater white matter damage, resulting in dysregulation of the frontal-striatal systems of the brain (Alexopoulos et al., 2008), which are critical for modulation of affect (Gunning-Dixon et al., 2008; Davidson et al., 2002). Although a relationship between poorer vascular health and white matter damage has been demonstrated in healthy adults (Jeerakathil et al., 2004; Herrmann et al., 2008) and individuals with MDD (Chen et al., 2006), to our knowledge, the relationship between vascular health and age of first MDE has not been studied. We therefore investigated the relationship between IMT and age of first MDE among 202 middle-aged and older adults with MDD.

2. Methods

2.1. Study design

The sample examined in this report represents baseline data obtained from a subset of individuals from a larger clinical trial of exercise and medication among middle-aged and older adults with MDD (Blumenthal et al., 2007). Exclusion criteria included a primary psychiatric diagnosis other than MDD, medical contraindications preventing participation in either the exercise or medication arm of the larger study (i.e., sertraline), and current treatment for MDD. No patient was on an anti-depressant at the time of this assessment. Participants were recruited from October 2000 to September 2005 and the study protocol was approved by a Duke Institutional Review Board.

2.2. Cerebrovascular risk factors

2.2.1. Framingham stroke risk profile—A modified version of the Framingham Stroke Risk Profile (FSRP), a risk assessment tool used to assess the risk of incident stroke, was used an index of cerebrovascular risk (Dagostino et al., 1994). Risk factors used to assess stroke risk include systolic blood pressure, use of antihypertensive therapy, diabetes mellitus, cigarette smoking, cardiovascular disease, and atrial fibrillation (Dagostino et al., 1994). Details of our cerebrovascular risk factor and IMT assessments have been previously reported (Smith et al., 2007). Because age served as a covariate in our statistical analyses, it was not included in calculating Framingham Stroke Risk Profile scores. Furthermore, left ventricular hypertrophy, a component of the original Framingham Stroke Risk Profile score, was not used in the current analysis because this information was not obtained for any participant.

2.2.2. Serum cholesterol—High-density lipoprotein (HDL-C) and low-density lipoprotein (LDL-C) cholesterol were assessed enzymatically (LabCorp, Research Triangle Park, NC). HDL-C was estimated by assay of the supernatant remaining after precipitation of serum LDL with dextran sulfate plus magnesium chloride. Participants fasted for 12 h prior to this assessment.

2.3. Measures of vascular health

2.3.1. Intima-media thickness (IMT) in carotid arteries—Carotid artery IMT was assessed by high-resolution B-mode ultrasound using an Acuson Aspen (Mountain View, CA)

vascular imaging system with 10 MHz linear array transducer. Ultrasound examinations of the far wall of the left and right common carotid arteries were used to acquire longitudinal images spanning 2 cm proximal to the carotid bulb. IMT of the far wall of the left and right common carotid arteries was measured over a 1 cm segment using Carotid Analyzer 5.0.5 (Medical Imaging Applications LLC, Iowa City, IA) edge detection software. Far wall measurements only were utilized as near wall measurements have been shown to have limited reliability (Wendelhag et al., 1991). Because left and right-sided IMT values were similar (mean left-sided IMT = .63 mm, SD = .15 mm; mean right-sided IMT = .63 mm, SD = .15 mm) and substantially intercorrelated ($r = .57$, $P < .0001$), these values were averaged to create one IMT value for each participant.

2.4. Assessment of depression

2.4.1. Structured clinical interview for the DSM-IV—The presence of MDD was determined by a trained clinical psychologist using the Structured Clinical Interview for the DSM-IV (SCID) (American Psychiatric Association, 2004). All participants met criteria for MDD based on Diagnostic and Statistical Manual-IV (American Psychiatric Association, 2004).

2.4.2. Hamilton rating scale for depression—Depression severity was assessed using the Hamilton Rating Scale for Depression (HRSD) (Williams, 1988), a 17-item clinical rating scale that assesses the severity of depressive symptoms such as changes in appetite, sleep, and depressed mood.

2.4.3. Age of onset of first MDE and number of previous MDEs—The SCID was supplemented with additional questions pertaining to the onset and treatment of the current MDE, as well as any prior MDEs. Previous MDEs were indexed as 0, 1, 2, or ≥ 3 MDEs prior to the current episode.

2.5. Statistical analysis

2.5.1. Data analysis—In order to determine the relationship between IMT, reported age of first MDE, and number of previous depressive episodes, we first examined the bivariate correlations between IMT and our depression variables. We then constructed two regression models in order to examine these relationships while controlling for relevant cardiovascular co-morbidities. In order to control for the effects of age in our analysis, IMT was examined as a dependent variable. Within these models, age at first MDE and number of previous MDEs were our predictors of interest while current age and cardiovascular co-morbidities served as covariates. Cardiovascular co-morbidities included the Framingham Stroke Risk Profile, current and previous smoking packs-per-year (PPY), physical activity (GODIN) (Godin and Shephard, 1985), body-mass index (BMI), HDL and LDL cholesterol, triglycerides, and history of chronic disease (e.g., stroke, cancer, and/or arthritis). As a supplementary analysis, we examined the association between IMT and depression severity, indexed by the HRSD. In this model, HRSD scores served as the predictor of interest with IMT as the dependent variable, controlling for cardiovascular co-morbidities. Multiple imputation based on the parametric maximum likelihood regression was used to account for missing data. Missing data was minimal (Harrell, 2001), with only 7 individuals (3.5%) missing IMT data and 5 (2.5%) missing data on age of first depressive episode. Model assumptions of additivity, linearity, and distribution of residuals were evaluated and found to be adequate before analysis.

3. Results

3.1. Sample characteristics

Participants ranged in age from 40 to 81 years of age (mean age = 51.7 years, SD = 7.6). As shown in Table 1, the majority of participants were female (75.7%) and Caucasian (67.8%), and almost half were college-educated (49.5%). Participants were in generally good health, as indexed by relatively low levels of FSRP (mean FSRP = 5.39, SD = 3.2), SBP (mean SBP = 124.2 mmHg, SD = 17.4), LDL cholesterol (mean LDL = 122.5 mg/dL, SD = 32.9), IMT (mean IMT = 0.63 mm, SD = .13), and higher HDL cholesterol (mean HDL = 56.9 mg/dL, SD = 16.0). The sample was relatively free of other co-morbidities such as diabetes (6.9%), arthritis (21.8%), current tobacco use (15.8%), history of cancer (5.5%), and history of stroke (2%).

3.2. Relationship of IMT, age of first MDE, and number of previous MDEs

In an unadjusted bivariate analysis, higher levels of IMT were associated with later ages of first MDE (b = .225, P = .0005) (Fig. 1). Every .10 mm increase in IMT was associated with an approximate 2.6 year later reported first MDE. As shown in Table 2, this relationship was only slightly attenuated when age, Framingham Stroke Risk Profile, BMI, HDL, LDL, triglycerides, history of chronic medical conditions, smoking history, and physical activity were controlled (b = .142, P = .028). Similarly, higher levels of IMT were associated with fewer previous MDEs (b = −.149, P = .020) and this effect remained significant in our multivariate model (b = −.140, P = .030). In contrast, IMT was not associated with depression severity (b = −.024, P = .720) and this effect was unchanged after controlling for cardiovascular co-morbidities.

4. Discussion

Results from the present analysis demonstrate that higher levels of IMT are associated with a later onset of first depressive episode and fewer previous depressive episodes, independent of cardiovascular co-morbidities. In contrast, IMT was unrelated to the severity of current depressive symptomatology. Our findings are consistent with previous observations in older patients demonstrating that elevated IMT is present in individuals with late-onset depression (Kim et al., 2006). Moreover, our findings are consistent with the notion that subclinical vascular disease may be associated with a later onset of MDD.

Our finding that higher levels of IMT may be associated with late-onset of depression is consistent with previous observations that elevated IMT is present in individuals with late-onset MDD (Kim et al., 2006). Greater IMT has been frequently observed among individuals with late-onset MDD (Kim et al., 2006; Campbell and Coffey, 2001) and is associated with increasing levels of white matter damage in this population (Chen et al., 2006). Moreover, recent work suggests that cerebral white matter damage, which often results from atherosclerosis, may independently predict the development of depressive symptoms (Teodorczuk et al., 2007)(Herrmann et al., 2008). Taken together, these findings are consistent with the hypothesis that cerebrovascular disease may be associated with an increased risk of incident depression among adults (Taylor et al., 2006; Alexopoulos, 2006; Alexopoulos et al., 1997).

The relationship between depression and subclinical vascular disease is complex and most likely results from overlapping pathogenic processes. In contrast to the typical clinical presentation of MDD, individuals with vascular depression exhibit greater cardiovascular risk factors, cognitive decrements, a later age of onset, and are less likely to report a family history of depression (Alexopoulos et al., 1997). Although subclinical vascular disease appears to precede depressive symptoms among individuals with vascular depression, depressive

symptoms in younger adults have been shown to predate vascular changes in some cases (Stewart et al., 2007). It is therefore possible that the observed relationship between greater IMT and late age of first MDE may have resulted from either pathophysiologic changes associated with atherosclerosis (Bruce and Musselman, 2005; Sherwood et al., 2005) or from patients chronically engaging in poor health behaviors. For example, previous studies have shown that greater psychosocial stress may be associated with poorer lifestyle choices (e.g., cigarette smoking, physical inactivity) (Green and Pope, 2000), which are associated with increased levels of IMT (Jeerakathil et al., 2004). However, the prevalence of smoking was relatively low in this study (16%) (Smith et al., 2007) and baseline physical activity level did not correlate with baseline depression severity in this sample.

This preliminary report has several limitations. Because our assessment of age at first MDE was based upon self-report, and was not corroborated by a third party, it is possible that patients were inaccurate in their recall of previous events. Second, with the exception of blood pressure and cholesterol measures, cerebrovascular risk factors also were based upon self-report and it is therefore possible that individuals with occult coronary disease might have gone undetected. Finally, because participants in the current study were volunteers and generally in good health, it is difficult to determine the generalizability of our findings to other outpatients with MDD (Zimmerman et al., 2002).

In summary, higher levels of IMT were associated with a later onset of first MDE and fewer previous depressive episodes among middle-aged and older adults with MDD. Future studies should investigate the prospective association between subclinical vascular disease, cerebral white matter damage, and MDD status to confirm this observation and elucidate the temporal relationship between these factors.

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Abbreviations

HRSD, Hamilton rating scale for depression; IMT, intima-media thickness; MDD, major depression; MDE, major depressive episode; SBP, systolic blood pressure.

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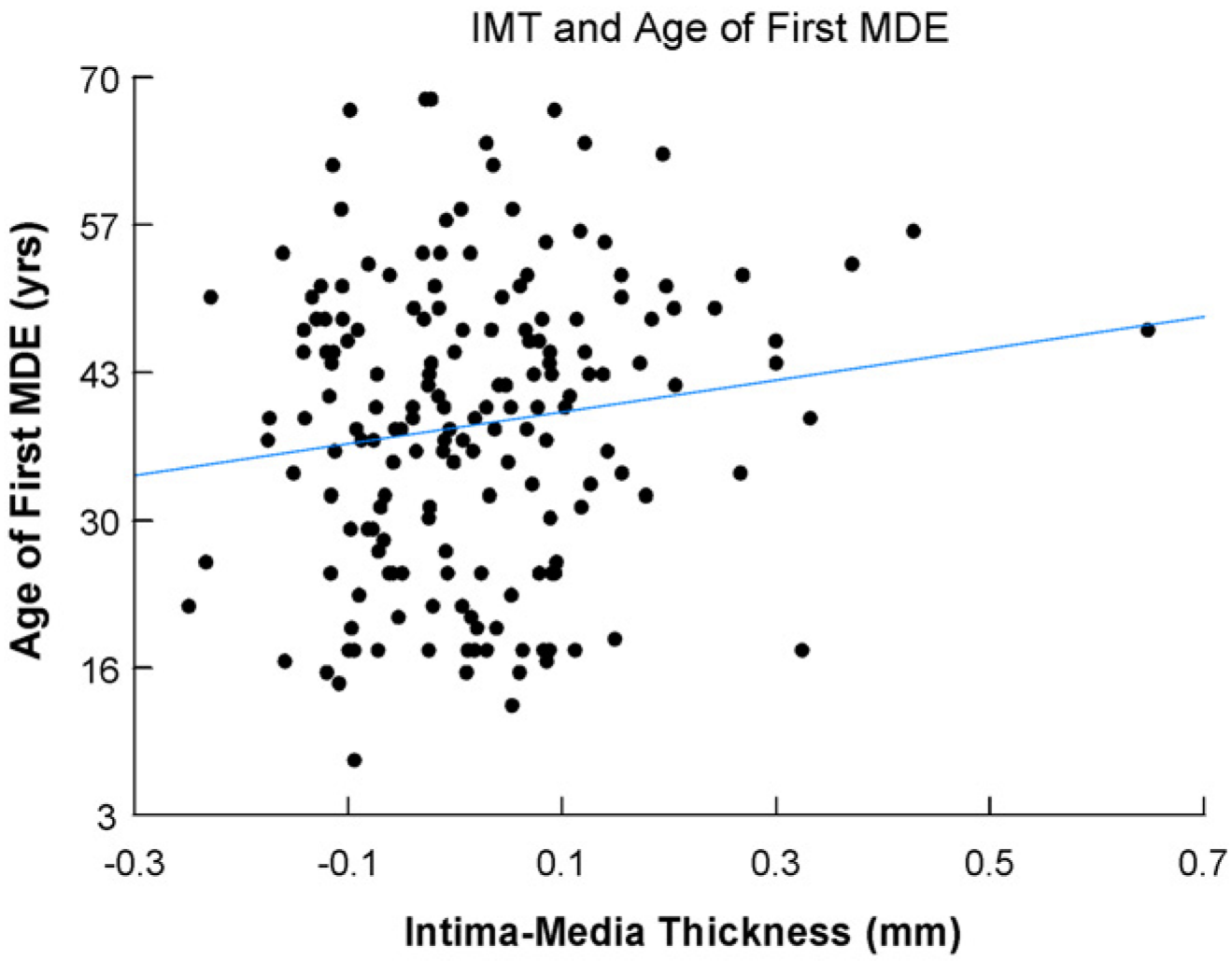

Fig. 1.
Intima-media thickness and age of first MDE. Higher IMT was associated with a later onset of first MDE (b = .225, P = .0005).

Table 1

Background characteristics.

Variable	Mean	SD
Age (year)	51.6	7.5
Gender (male), *n* (%)	48 (24)	
Caucasians, *n* (%)	134 (68)	
Education (college graduate), *n* (%)	100 (51)	
HRSD	17	4.3
Married, *n* (%)	75	49
IMT (mm)	0.63	0.13
Current smoker, *n* (%)	32 (16)	
Previous smoker (excluding current use), *n* (%)	65 (38)	
SBP (mmHg)	124	18
DBP (mmHg)	79	10
BP-lowering medications, *n* (%)	47 (23)	
Total cholesterol (mg/dL)	207	41
LDL total (mg/dL)	122	33
HDL total (mg/dL)	56.9	15.8
Lipid-lowering medications, *n* (%)	17 (8)	
BMI (kg/m^2)	30.1	7.1
GODIN Exercise	9.5	10.3
Framingham Risk Profile Score	5.4	3.2
Age of first depressive episode (year)	38.3	13.6
Previous depressive episodes, *n* (%)		
(0)	69 (34.2)	
(1)	48 (23.8)	
(2)	15 (7.4)	
(≥3)	70 (34.7)	

Note: HRSD indicates Hamilton rating scale for depression; IMT indicates intima-medial thickness; SBP indicates systolic blood pressure; DBP indicates diastolic blood pressure; mmHg indicates millimeters of mercury; LDL indicated low-density lipoprotein; HDL indicates high-density lipoprotein; BMI indicated body mass index.

Table 2

Results of linear regression model predicting IMT.

Variable (interquartile range)	b	*P*-value
Age (10)	.177	.006
FSRP (2)	.078	.224
Smoking, PPY (364)	.048	.470
GODIN (15)	.079	.249
HDL (22)	−.114	.076
LDL (43)	−.064	.328
BMI (9.3)	.228	<.001
Triglycerides (101)	−.046	.476
Chronic co-morbidities (Y)	.058	.368
Age at First MDD (19)	.142	.028

*Note: Continuous predictors were rescaled by dividing the raw unscaled value by the interquartile range of the predictor. The scaling factor is shown in the parentheses to the right of the name of the predictor in column 1. For example, the regression coefficient for age represents the expected change in IMT for every 10-year increase in age. An alternative interpretation of is that it compares a “typical” person in the middle of the upper half of the predictor distribution with a “typical” person in the middle of the lower half of the predictor distribution. FSRP = Framingham Stroke Risk Profile; GODIN = Godin Leisure-Time Exercise. Chronic co-morbidities = stroke, cancer, and arthritis.